



06/16/97

201.06(a)

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714765 U.S. PTO  
06/97

## TYPES, CROSS-NOTING, AND STATUS OF APPLICATION

PTO/SB/13 \*\*&gt;(01-96)&lt;

Approved for use through 05/31/96. OMB 0651-0033  
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

## REQUEST FOR FILING A PATENT APPLICATION UNDER 37 CFR 1.60

DOCKET NUMBER	ANTICIPATED CLASSIFICATION OF THIS APPLICATION		PRIOR APPLICATION EXAMINER	ART UNIT
	CLASS	SUBCLASS		
16955DIVCON CIPCON (AP)			Mary Cebulak	1209

Address to:

&gt;Assistant&lt; Commissioner \* &gt;for&lt; Patents \*\*

Washington, D.C. 20231

This is a request for filing a  continuation  divisional application under 37 CFR 1.60, of pending prior application Number 08/605,567, filed on 2/22/1996 entitled NON-ACIDIC CYCLOPENTANE HEPTANOIC ACID, 2-CYCLOALKYL OR ARYLAalkyl DERIVATIVES AS THERAPEUTIC AGENTS

1. Enclosed is a copy of the latest inventor-signed prior application, including a copy of the oath or declaration showing the original signature or an indication it was signed. I hereby verify that the papers are a true copy of the latest signed prior application number 08/605,567, and further that all statements made herein of my own knowledge are true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

CLAIMS	(1) FOR	(2) NUMBER FILED	(3) NUMBER EXTRA	(4) RATE	(5) CALCULATIONS
	TOTAL CLAIMS <small>37 CFR 1.14(c))</small>	21 - 20 =	1	x \$ 22 =	\$ 22.00
	INDEPENDENT CLAIMS <small>37 CFR 1.14(c))</small>	4 - 3 =	1	x \$ .80 =	80.00
	MULTIPLE DEPENDENT CLAIMS (if applicable) <small>37 CFR 1.14(c))</small>			+ \$	
				BASIC FEE <small>37 CFR 1.14(c))</small>	+ 770.00
				Total of above Calculations =	872.00
				Reduction by 50% for filing by small entity (Note 37 CFR 1.9, 1.27, 1.28).	
				TOTAL =	

2.  A verified statement to establish small entity status under 37 CFR 1.9 and 1.27
  - is enclosed.
  - was filed in prior application number 08/605,567 / \_\_\_\_\_, and such status is still proper and desired (37 CFR 1.28(a)).
3.  The Commissioner is hereby authorized to charge any fees which may be required under 37 CFR 1.16 and 1.17, or credit any overpayment to Deposit Account No. 01-0885. A duplicate copy of this sheet is enclosed.
4.  A check in the amount of \$ \_\_\_\_\_ is enclosed.
5.  Cancel in this application original claims 2 through 25 of the prior application before calculating the filing fee. (At least one original independent claim must be retained for filing purposes.)
6.  The inventor(s) of the invention being claimed in this application is (are): David F. Woodward; Steven W. Andrews; Robert M. Burk and Michael E. Garst
7.  This application is being filed by less than all the inventors named in the prior application. In accordance with 37 CFR 1.60(b), the Commissioner is requested to delete the name(s) of the following person or persons who are not inventors of the invention being claimed in this application:
8.  Amend the specification by inserting before the first line the sentence: "This application is a  continuation  division of application number 08/605,567, filed 2/22/1996 \* (status, abandoned, pending, etc.)." \*pending

{Page 1 of 2}

Burden Hour Statement: This form is estimated to take \*\* >0.5 hour< to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete the form should be sent to the \*\* >Chief Information Officer<, Patent and Trademark Office, Washington, D.C. 20231 \*\*. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, D.C. 20231.

MANUAL OF PATENT EXAMINING PROCEDURE

**201.06(a)**

PTO/SB/13 \*\*> (01-96) <

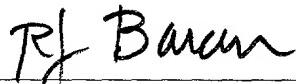
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Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

**(REQUEST FOR FILING A PATENT APPLICATION UNDER 37 CFR 1.60, PAGE 2)**

9.  New formal drawings are enclosed.
10.  Priority of foreign application number \_\_\_\_\_, filed on \_\_\_\_\_ in \_\_\_\_\_  
> is claimed under 35 U.S.C. 119(a)-(d). <  
 The certified copy has been filed in prior application number \_\_\_ / \_\_\_\_\_, filed \_\_\_\_\_
11.  A preliminary amendment is enclosed.
12.  The prior application is assigned of record to Allergan
13.  Also enclosed: Form PTO 1449 and Information Disclosure Statement
14.  The power of attorney in the prior application is to: Robert J. Baran
- a.  The power of attorney appears in the original papers in the prior application.
- b.  Since the power does not appear in the original papers, a copy of the power in the prior application is enclosed.
- c.  Address all future correspondence to: (May only be completed by applicant, or attorney or agent of record.)  
Robert J. Baran (T2-2E)  
Allergan, Inc.  
2525 Dupont Drive  
Irvine, CA 92612-1599

June 16, 1997

Date



Signature

Robert J. Baran

Typed or printed name

- Inventor(s)  
 Assignee of complete interest >. Certification under 37 CFR 3.73(b) is enclosed. <  
 Attorney or agent of record  
 Filed under 37 CFR 1.34(a)  
Registration number if acting under 37 CFR 1.34(a). 25,806



PATENT 06/16/97

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of

Woodward et al

Serial No: n/a

Filed: Submitted herewith

For: CYCLOPENTANE HEPTANOIC  
ACID, 2-CYCLOALKYL OR  
ARYLALKYL DERIVATIVES AS  
THERAPEUTIC AGENTS

Group Art Unit: 1209

Examiner: M. Cebulak

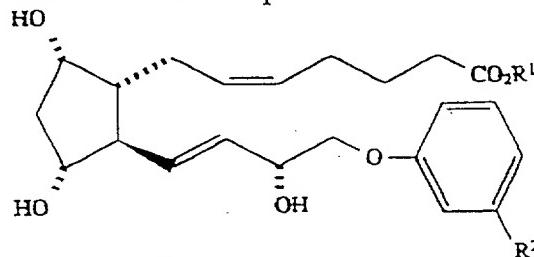
PRELIMINARY AMENDMENT

Honorable Commissioner of Patents and Trademarks  
Washington, D.C. 20231

Dear Sir:

Please cancel claims 2 through 25.

26. (New Claim) A method of treating glaucoma and ocular hypertension which comprises topically administering to the affected eye a therapeutically effective amount of a compound of formula:



wherein R<sup>1</sup> =hydrogen, a cationic salt moiety, a pharmaceutically acceptable amine moiety or C<sub>1</sub>-C<sub>12</sub> alkyl cycloalkyl or aryl; and R<sup>2</sup> = Cl or CF<sub>3</sub>.

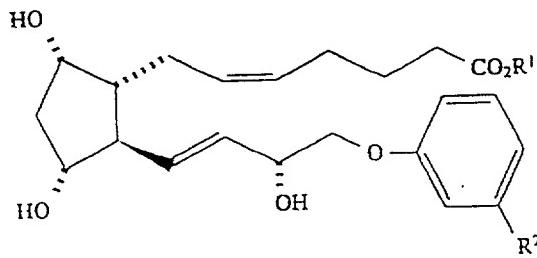
27. (New Claim) The method of claim 26, wherein R<sup>1</sup> is selected from the group consisting of H, CH<sub>3</sub>, CH(CH<sub>3</sub>)<sub>2</sub> and C(CH<sub>3</sub>)<sub>3</sub>.

28. (New Claim) The method of claim 26, wherein R<sup>1</sup> is selected from the group consisting of Na<sup>+</sup> and CH<sub>3</sub>N<sup>+</sup>(CH<sub>2</sub>OH)<sub>3</sub>.

29. (New Claim) The method of claim 26, wherein R<sup>2</sup> is Cl.
30. (New Claim) The method of claim 27, wherein R<sup>2</sup> is CF<sub>3</sub>.
31. (New Claim) The method of claim 26, wherein between about 0.001 and about 1000 µg/eye of a compound of formula (I) is administered.
32. (New Claim) The method of claim 31, wherein between about 0.01 and about 100 µg/eye of a compound of formula (I) is administered.

33. (New Claim) The method of claim 31, wherein between about 0.05 and about 10 µg/eye of a compound of formula (I) is administered.

34. (New Claim) A topical ophthalmic composition for the treatment of glaucoma and ocular hypertension in primates, comprising a therapeutically effective amount of a compound of formula:



wherein: R<sup>1</sup> = hydrogen, a cationic salt moiety, a pharmaceutically acceptable amine moiety or C<sub>1</sub>-C<sub>12</sub> alkyl, cycloalkyl or aryl; and R<sup>2</sup> = Cl or CF<sub>3</sub>.

35. (New Claim) The composition of claim 34, wherein R<sup>1</sup> is selected from the group consisting of H, CH<sub>3</sub>, CH(CH<sub>3</sub>)<sub>2</sub> and C(CH<sub>3</sub>)<sub>3</sub>.

36. (New Claim) The composition of claim 34, wherein R<sup>1</sup> is selected from the group consisting of Na<sup>+</sup> and CH<sub>3</sub>N<sup>+</sup>(CH<sub>2</sub>OH)<sub>3</sub>.

37. (New Claim) The composition of claim 34, wherein R<sup>2</sup> is Cl.

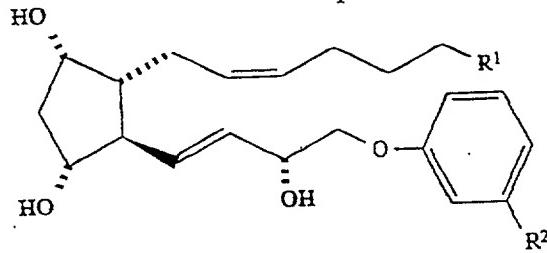
38. (New Claim) The composition of claim 34, wherein R<sup>2</sup> is CF<sub>3</sub>.

39. (New Claim) The composition of claim 34, wherein between about 0.001 and about 100 µg/eye of a compound of formula (I) is administered.

40. (New Claim) The composition of claim 39, wherein between about 0.01 and about µg/eye of a compound of formula (I) is administered.

41. (New Claim) The composition of claim 40, wherein between about 0.05 and about 10 µg/eye of a compound of formula (I) is administered.

42. (New Claim) A method of treating glaucoma and ocular hypertension, which comprises topically administering to the affected eye a therapeutically effective amount of a compound of formula:



wherein: R<sup>1</sup> = a pharmaceutically acceptable ester moiety; and R<sup>2</sup> = Cl or CF<sub>3</sub>.

43. (New Claim) The method of claim 42, wherein R<sup>2</sup> is Cl.

44. (New Claim) The method of claim 42, wherein R<sup>2</sup> is CF<sub>3</sub>.

45. (New Claim) The method of claim 42, wherein between about 0.001 and about 1000 µg/eye of a compound of formula (I) is administered.

REMARKS

The present invention relates to certain cyclopentane heptanoic acid, 2-arylalkyl compounds, which comprise an omega chain chlorophenoxy or trifluoromethylphenoxy and are useful in treating glaucoma and ocular hypertension and pharmaceutical compositions useful in such treatment.

The applicants have filed claims 26 through 45 to specifically copy claims 1 through 20 of U.S. Patent No. 5,510,383 ("Bishop") and request that the Examiner declare an interference to determine the priority of invention as to the subject matter of these added claims. The claims copied from Bishop are supported in the present specification as follows:

<u>Bishop, Claim 1</u> <u>Woodward Claim 26</u>	<u>Support in</u> <u>Present Application</u>
R <sup>1</sup> is hydrogen	Claim 1, X is OR <sup>4</sup> and R <sup>4</sup> may be hydrogen
R <sup>1</sup> is C <sub>1</sub> -C <sub>12</sub> alkyl, etc.	Claim 1, R <sup>4</sup> may be lower alkyl
R <sup>1</sup> is a pharmaceutically acceptable amine	Claim 1, compound of formula I, includes pharmaceutically-acceptable salts
R <sup>1</sup> is a cationic salt	Claim 1, compound of formula I, includes pharmaceutically-acceptable salts
R <sup>2</sup> is Cl or CF <sub>3</sub>	Claim 4, Y <sup>1</sup> is Cl or trifluoromethyl
<u>Bishop Claim 2</u> <u>Woodward Claim 27</u>	Claim 1 R <sup>4</sup> may be hydrogen or lower alkyl. See also, page 10, lines 25 and 26 wherein lower alkyl includes methyl, propyl and butyl
R <sup>1</sup> is H, CH <sub>3</sub> , CH(CH <sub>3</sub> ) <sub>2</sub>	

Docket No. 16955DIVCONCIPCON(AP)

R<sup>1</sup> is H, CH<sub>3</sub>, CH(CH<sub>3</sub>)<sub>2</sub>  
and C(CH<sub>3</sub>)<sub>3</sub>

methyl, propyl and butyl

Bishop Claim 3  
Woodward Claim 28

R<sup>1</sup> is Na<sup>+</sup> or  
CH<sub>3</sub>N<sup>+</sup>(CH<sub>2</sub>OH)<sub>3</sub>

Claim 1 includes pharmaceutically-acceptable salts. See also, page 13, line 5 wherein salt includes alkali metal salts

Bishop Claim 4  
Woodward Claim 29

R<sup>2</sup> is Cl

See claim 4 wherein Y<sup>1</sup> is Cl

Bishop Claim 5  
Woodward Claim 30

R<sup>2</sup> is CF<sup>3</sup>

See claim 4 wherein Y<sup>1</sup> is trifluoromethyl

Bishop Claims 6-8  
Woodward's Claims 31-33

between about 0.001  
and about 1000  
μg/eye of compound  
is administered

See page 13, lines 12-14  
"therapeutically efficient amount  
is between about 0.0001 and 5% (w/v),  
preferably about 0.001 to about 1.0%  
w/v"

Bishop Claims 9-16  
Woodward's Claims 34-41

Cover ophthalmic compositions useful in the method of claims 1-9 of Bishop and claims 26-33 of Woodward, respectively. The limitations of these claims mirror the limitations of the previously discussed method claims

Docket No. 16955DIVCONCIPCON(AP)

Bishop Claim 17  
Woodward Claim 42

R<sup>1</sup> is a pharmaceutically acceptable ester moiety

See Claim 1, wherein Z is =O and X is -OR<sup>4</sup>, wherein R<sup>4</sup> is a lower alkyl

R<sup>2</sup> is Cl or CF<sub>3</sub>

See Claim 4 wherein Y<sup>1</sup> is Cl or trifluoromethyl

Bishop Claims 18-20  
Woodward's Claims 43-45

(See discussion above.)

Respectfully Submitted,

*RF Baran*

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 Irvine, CA 92612-1599

Express Mail Number: EM272469880US

Date of Deposit June 16, 1997

I HEREBY CERTIFY THAT THIS PAPER IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE "EXPRESS MAIL POST OFFICE TO ADDRESSEE" SERVICE UNDER 37 CFR 1.10 ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO COMMISSIONER OF PATENTS AND TRADEMARKS, WASHINGTON, D.C. 20231 on 6/16/97 (Date)

*Bonnie Ferguson*  
 Bonnie Ferguson

6/16/97  
 Date

16955DIV2CIP

**NON-ACIDIC CYCLOPENTANE HEPTANOIC ACID,  
2-CYCLOALKYL OR ARYLALKYL DERIVATIVES  
AS THERAPEUTIC AGENTS**

5

**Crossreference to Related Applications**

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This patent application is a continuation-in-part of U.S. Patent Application Serial No. 08/371,339, filed on January 11, 1995 which is a continuation of U.S. Patent Application Serial No. 08/154,244 which was filed on November 18, 1993, which is a divisional of U.S. Patent Application Serial No. 07/948,056, filed on September 21, 1992, now U.S. Patent No. 5,352,708 issued on October 4, 1994, all of which are hereby incorporated by reference.

15

**Background of the Invention**

**1. Field of the Invention**

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The present invention provides cyclopentane heptanoic acid, 2-cycloalkyl or arylalkyl compounds, which may be substituted in the 1-position with amino, amido, ether or ester groups, e.g., a 1-OH cyclopentane heptanoic acid, 2-(cycloalkyl or arylalkyl) compound. The cyclopentane heptanoic acid, 2-(cycloalkyl or arylalkyl) compounds of the present invention are potent ocular hypotensives, and are particularly suitable for the management of glaucoma. Moreover, the cyclopentane heptanoic, 2-(cycloalkyl or arylalkyl) compounds of this invention are smooth muscle relaxants with broad application in systemic hypertensive and pulmonary diseases; smooth muscle relaxants with application in gastrointestinal disease, reproduction, fertility, incontinence, shock, etc.

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## 2. Description of the Related Art

5           Ocular hypotensive agents are useful in the treatment of a number of various ocular hypertensive conditions, such as post-surgical and post-laser trabeculectomy ocular hypertensive episodes, glaucoma, and as presurgical adjuncts.

10          Glaucoma is a disease of the eye characterized by increased intraocular pressure. On the basis of its etiology, glaucoma has been classified as primary or secondary. For example, primary glaucoma in adults (congenital glaucoma) may be either open-angle or acute or chronic angle-closure. Secondary glaucoma results from pre-existing ocular diseases such as uveitis, intraocular tumor or an enlarged cataract.

15          The underlying causes of primary glaucoma are not yet known. The increased intraocular tension is due to the obstruction of aqueous humor outflow. In chronic open-angle glaucoma, the anterior chamber and its anatomic structures appear normal, but drainage of the aqueous humor is impeded. In acute or chronic angle-closure glaucoma, the anterior chamber is shallow, the filtration angle is narrowed, and the iris may obstruct the trabecular meshwork at the entrance of the canal of Schlemm. Dilation of the pupil may push the root of the iris forward against the angle, and may produce pupillary block and thus precipitate an acute attack. Eyes with narrow anterior chamber angles are predisposed to acute angle-closure glaucoma attacks of various degrees of severity.

20          Secondary glaucoma is caused by any interference with the flow of aqueous humor from the posterior chamber into the anterior chamber and subsequently, into the canal of Schlemm. Inflammatory disease of the anterior segment may prevent aqueous escape by causing complete posterior synechia in iris bombe and may plug the drainage channel with exudates. Other common causes are intraocular tumors, enlarged cataracts, central retinal vein occlusion, trauma to the eye, operative procedures and intraocular hemorrhage.

25          Considering all types together, glaucoma occurs in about 2% of all persons over the age of 40 and may be asymptotic for years before progressing to rapid loss of vision. In cases where surgery is not

DEPARTMENT OF HOMELAND SECURITY  
FEDERAL BUREAU OF INVESTIGATION

indicated, topical b-adrenoreceptor antagonists have traditionally been the drugs of choice for treating glaucoma.

Prostaglandins were earlier regarded as potent ocular hypertensives; however, evidence accumulated in the last two decades shows that some prostaglandins are highly effective ocular hypotensive agents and are ideally suited for the long-term medical management of glaucoma. (See, for example, Starr, M.S. Exp. Eye Res. 1971, 11, pp. 170-177; Bito, L. Z. Biological Protection with Prostaglandins Cohen, M. M., ed., Boca Raton, Fla, CRC Press Inc., 1985, pp. 231-252; and Bito, L. Z., Applied Pharmacology in the Medical Treatment of Glaucomas Drance, S. M. and Neufeld, A. H. eds., New York, Grune & Stratton, 1984, pp. 477-505). Such prostaglandins include PGF<sub>2a</sub>, PGF<sub>1a</sub>, PGE<sub>2</sub>, and certain lipid-soluble esters, such as C<sub>1</sub> to C<sub>5</sub> alkyl esters, e.g. 1-isopropyl ester, of such compounds.

In the United States Patent No. 4,599,353 certain prostaglandins, in particular PGE<sub>2</sub> and PGF<sub>2a</sub> and the C<sub>1</sub> to C<sub>5</sub> alkyl esters of the latter compound, were reported to possess ocular hypotensive activity and were recommended for use in glaucoma management.

Although the precise mechanism is not yet known, recent experimental results indicate that the prostaglandin-induced reduction in intraocular pressure results from increased uveoscleral outflow [Nilsson et al., Invest. Ophthalmol. Vis. Sci. 28(suppl), 284 (1987)].

The isopropyl ester of PGF<sub>2a</sub> has been shown to have significantly greater hypotensive potency than the parent compound, which was attributed to its more effective penetration through the cornea. In 1987 this compound was described as "the most potent ocular hypotensive agent ever reported." [See, for example, Bito, L. Z., Arch. Ophthalmol. 105, 1036 (1987), and Siebold et al., Prodrug 5, 3 (1989)].

Whereas prostaglandins appear to be devoid of significant intraocular side effects, ocular surface (conjunctival) hyperemia and foreign-body sensation have been consistently associated with the topical ocular use of such compounds, in particular PGF<sub>2a</sub> and its prodrugs, e.g. its 1-isopropyl ester, in humans. The clinical potential of prostaglandins in the management of conditions associated with

increased ocular pressure, e.g. glaucoma, is greatly limited by these side effects.

5        Certain phenyl and phenoxy mono, tri and tetra nor prostaglandins and their 1-esters are disclosed in European Patent Application 0,364,417 as useful in the treatment of glaucoma or ocular hypertension.

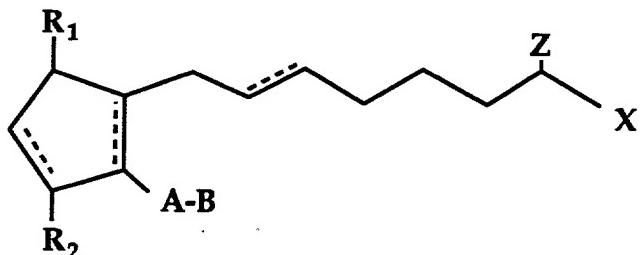
10      In a series of co-pending United States patent applications assigned to Allergan, Inc. prostaglandin esters with increased ocular hypotensive activity accompanied with no or substantially reduced side-effects are disclosed. The co-pending USSN 386,835 (filed 27 July 1989), relates to certain 11-acyl-prostaglandins, such as 11-pivaloyl, 11-acetyl, 11-isobutyryl, 11-valeryl, and 11-isovaleryl PGF<sub>2a</sub>. Intraocular pressure reducing 15-acyl prostaglandins are disclosed in the co-pending application USSN 357,394 (filed 25 May 1989). Similarly, 11,15- 9,15- and 9,11-diesters of prostaglandins, for example 11,15-dipivaloyl PGF<sub>2a</sub> are known to have ocular hypotensive activity. See the co-pending patent applications USSN No. 385,645 filed 27 July 1990, now U.S. Patent No. 4,494,274; 584,370 which is a continuation of USSN No. 386,312, and 585,284, now U.S. Patent No. 5,034,413 which is a continuation of USSN 386,834, where the parent applications were filed on 27 July 1989. The disclosures of these patent applications are hereby expressly incorporated by reference.

25      Summary of the Invention

30      We have found that certain cyclopentane heptanoic acid, 2-cycloalkyl or arylalkyl compounds and derivatives thereof wherein the carboxylic acid group is replaced by a non-acidic substituent have pronounced effects on smooth muscle and are potent ocular hypotensive agents. We have further found that such compounds, in certain instances, may be significantly more potent than their respective parent compounds and, in the case of glaucoma surprisingly, cause no or significantly lower ocular surface hyperemia than the parent compounds.

35      The present invention relates to methods of treating cardiovascular, pulmonary-respiratory, gastrointestinal, reproductive,

allergic disease, shock and ocular hypertension which comprises administering an effective amount of a cyclopentane heptanoic acid, 2-cycloalkyl or arylalkyl compound represented by the formula I



R<sub>2</sub>

5 wherein the dashed bonds represent a single or double bond which can be in the cis or trans configuration, A is an alkylene or alkenylene radical having from two to six carbon atoms, which radical may be interrupted by one or more oxide radicals and substituted with one or more hydroxy, oxo, alkyloxy or alkylcarboxy groups wherein said alkyl radical comprises from one to six carbon atoms; B is a cycloalkyl radical having from three to seven carbon atoms, or an aryl radical, selected from the group consisting of hydrocarbyl aryl and heteroaryl radicals having from four to ten carbon atoms wherein the heteroatom is selected from the group consisting of nitrogen, oxygen and sulfur atoms; X is a radical selected from the group consisting of -OR<sup>4</sup> and -N(R<sup>4</sup>)<sub>2</sub> wherein R<sup>4</sup> is selected from the group consisting of hydrogen, a lower alkyl radical having from one to six

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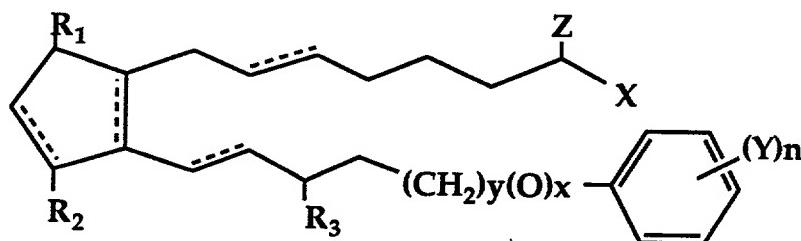
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$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}^5-\text{C}- \end{array}$        $\begin{array}{c} \text{O} \\ \parallel \\ \text{O}-\text{C}- \end{array}$

carbon atoms, R<sup>5</sup>-C- or R<sup>5</sup>-O-C-- wherein R<sup>5</sup> is a lower alkyl radical having from one to six carbon atoms; Z is =O or represents 2 hydrogen radicals; one of R<sub>1</sub> and R<sub>2</sub> is =O, -OH or a -O(CO)R<sub>6</sub> group, and the other one is -OH or -O(CO)R<sub>6</sub>, or R<sub>1</sub> is =O and R<sub>2</sub> is H, wherein R<sub>6</sub> is a saturated or unsaturated acyclic hydrocarbon group having from 1 to about 20 carbon atoms, or -(CH<sub>2</sub>)<sub>m</sub>R<sub>7</sub> wherein m is 0 or an integer of from 1 to 10, and R<sub>7</sub> is cycloalkyl radical, having from three to seven carbon atoms, or a hydrocarbyl aryl or heteroaryl radical, as defined above, or a pharmaceutically-acceptable salt thereof, provided, however, that when B is not substituted with a pendant heteroatom-containing radical, and Z is =O, then X is not

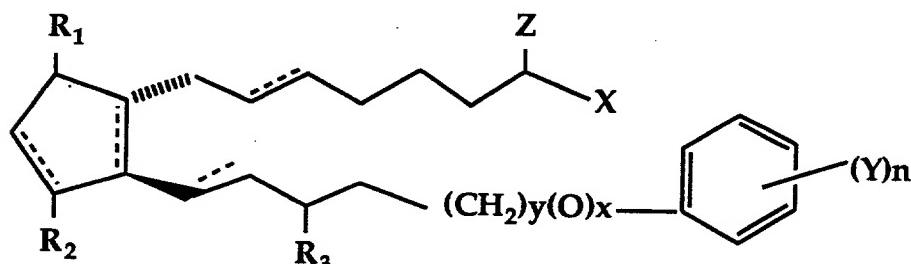
-OR<sup>4</sup>. (That is, the cycloalkyl or hydrocarbyl aryl or heteroaryl radical is not substituted with a pendant radical having an atom other than carbon or hydrogen.)

5 More preferably the method of the present invention comprises administering a cyclopentane heptanoic acid, 2-(phenyl alkyl or phenoxyalkyl) represented by the formula II



10 wherein y is 0 or 1, x is 0 or 1 and x and y are not both 1, Y is a radical selected from the group consisting of alkyl, halo, e.g. fluoro, chloro, etc., nitro, amino, thiol, hydroxy, alkyloxy, alkylcarboxy, halo substituted alkyl wherein said alkyl radical comprises from one to six carbon atoms, etc. and n is 0 or an integer of from 1 to about 3 and R<sub>3</sub> is =O, -OH or -O(CO)R<sub>6</sub> wherein R<sub>6</sub> is as defined above. Preferably, n is 1 or 2.

15 Preferably the compound used in the above method of treatment is a compound of formula (III).

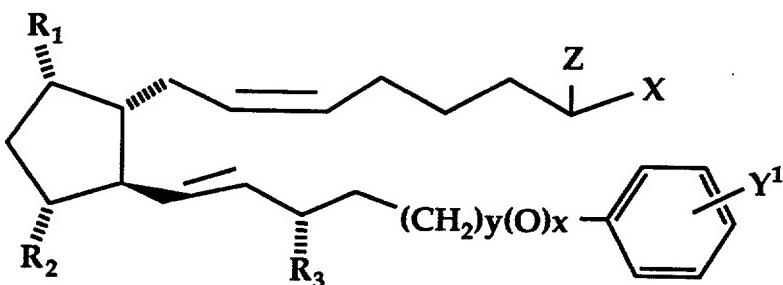


20 wherein hatched lines indicate a configuration, solid triangles are used to indicate  $\beta$  configuration

In another aspect, the present invention relates to a method of treating cardiovascular, pulmonary-respiratory, gastrointestinal, reproductive and allergic diseases, shock and ocular hypertension

which comprises administering to a subject a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (IV)

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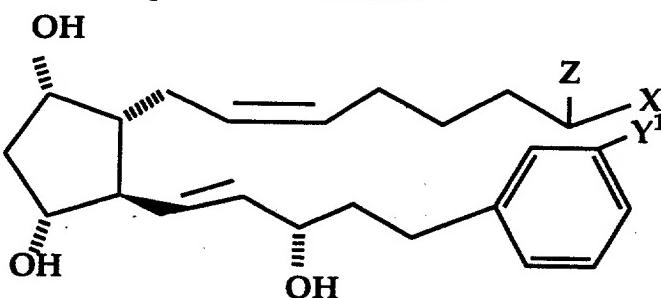


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wherein Y<sup>1</sup> is Cl or trifluoromethyl and the other symbols and substituents are as defined above, in combination with a pharmaceutical carrier.

15

Finally, the method of the present invention relates to a method of treating cardiovascular, pulmonary-respiratory, gastrointestinal, reproductive and allergic diseases, shock and ocular hypertension which comprises administering to a subject a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula V



and the 9-and/or 11- and/or 15 esters thereof.

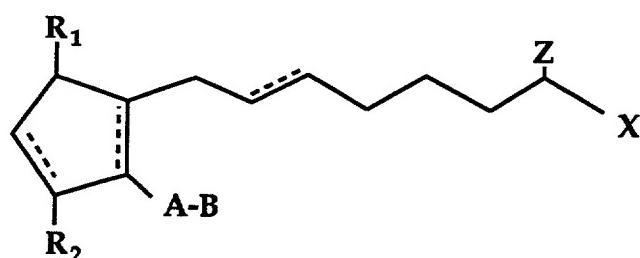
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In a further aspect, the present invention relates to pharmaceutical compositions comprising a therapeutically effective amount of a compound of formulae (I), (II), (III), (IV) or (V) wherein the symbols have the above meanings, or a pharmaceutically acceptable salt thereof in admixture with a non-toxic, pharmaceutically acceptable liquid vehicle.

5 In a still further aspect, the present invention relates to cyclopentane heptanoic acid, 2-cycloalkyl or arylalkyl compounds of the above formulae, wherein the substituents and symbols are as defined hereinabove, or a pharmaceutically acceptable salt of such compounds.

#### Detailed Description of the Invention

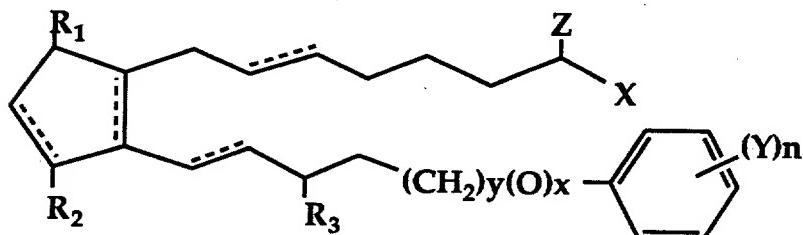
10 The present invention relates to the use of cyclopentane heptanoic acid, 2-cycloalkyl or arylalkyl compounds as therapeutic agents, e.g. as ocular hypotensives. These therapeutic agents are represented by compounds having the formula I,



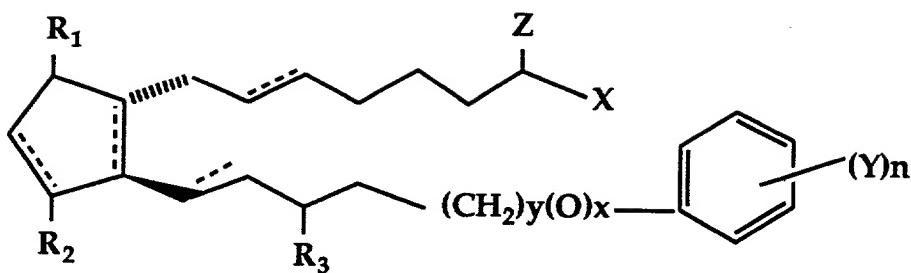
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as defined above. The preferred nonacidic cyclopentane heptanoic acid, 2-(phenyl alkyl or phenoxyalkyl) compounds used in accordance with the present invention are encompassed by the following structural formula (II)

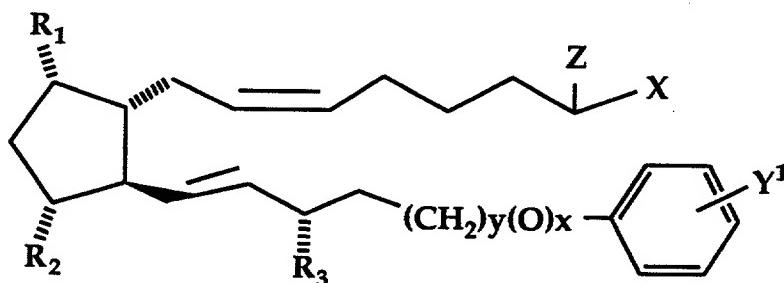
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wherein the substituents and symbols are as hereinabove defined. More preferably the compounds are represented by formula (III).

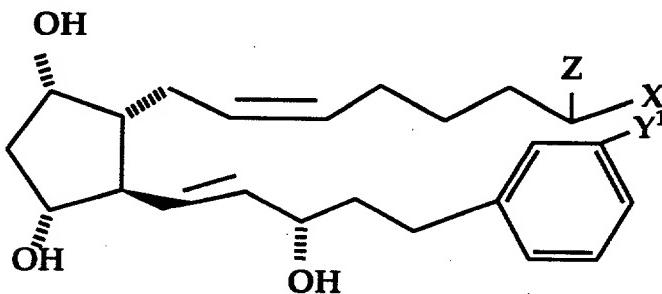


wherein the substituents and symbols are as defined above. More preferably, the compounds utilized in the present invention are compounds represented by the formula (IV)



wherein the substituents and the symbols are as defined above.

Most preferably the present invention utilizes the novel compounds of the formula (V)



15

and their 9- and/or 11- and/or 15-esters.

In all of the above formulae, as well as in those provided hereinafter, the dotted lines on bonds between carbons 5 and 6 (C-5), between carbons 13 and 14 (C-13), between carbons 8 and 12 (C-8), and

5 between carbons 10 and 11 (C-10) indicate a single or a double bond which can be in the cis or trans configuration. If two solid lines are used that indicates a specific configuration for that double bond. Hatched lines at positions C-9, C-11 and C-15 indicate the  $\alpha$  configuration. If one were to draw the  $\beta$  configuration, a solid 10 triangular line would be used.

10 In the compounds used in accordance with the present invention, compounds having the C-9 or C-11 or C-15 substituents in the  $\alpha$  or  $\beta$  configuration are contemplated. As hereinabove mentioned, in all formulas provided herein broken line attachments to the cyclopentane ring indicate substituents in the  $\alpha$  configuration. Thickened solid line attachments to the cyclopentane ring indicate substituents in the  $\beta$  configuration. Also, the broken line attachment 15 of the hydroxyl group or other substituent to the C-11 and C-15 carbon atoms signifies the  $\alpha$  configuration.

20 For the purpose of this invention, unless further limited, the term "alkyl" refers to alkyl groups having from one to ten carbon atoms, the term "cycloalkyl" refers to cycloalkyl groups having from three to seven carbon atoms, the term "aryl" refers to aryl groups having from four to ten carbon atoms. The term "saturated or unsaturated acyclic hydrocarbon group" is used to refer to straight or branched chain, saturated or unsaturated hydrocarbon groups having from one to about 6, preferably one to about 4 carbon atoms. Such groups include alkyl, alkenyl and alkynyl groups of appropriate lengths, and preferably are alkyl, e.g. methyl, ethyl, propyl, butyl, 25 pentyl, or hexyl, or an isomeric form thereof.

30 The definition of  $R_6$  may include a cyclic component,  $-(CH_2)_mR_7$ , wherein  $n$  is 0 or an integer of from 1 to 10,  $R_7$  is an aliphatic ring from about 3 to about 7 carbon atoms, or an aromatic or heteroaromatic ring. The "aliphatic ring" may be saturated or unsaturated, and preferably is a saturated ring having 3-7 carbon atoms, inclusive. As an aromatic ring,  $R_7$  preferably is phenyl, and the heteroaromatic rings have oxygen, nitrogen or sulfur as a heteroatom, i.e.  $R_7$  may be thienyl, furanyl, pyridyl, etc. Preferably  $m$  is 0 or an integer of from 1 to 4.

Z is =O or represents two hydrogen atoms.

X may be selected from the group consisting of -OR<sup>4</sup> and -N(R<sup>4</sup>)<sub>2</sub> wherein R<sup>4</sup> is selected from the group consisting of hydrogen, a lower alkyl radical having from one to six

5

carbon atoms, R<sup>5</sup>-C=O or R<sup>5</sup>-O-C=O wherein R<sup>5</sup> is a lower alkyl radical having from one to six carbon atoms.

10

Preferred representatives of the compounds within the scope of the present invention are the compounds of formula V wherein X is -OH, i.e. cyclopentane heptenoic acid, 5-cis-2-(3 $\alpha$ -hydroxy-4-m-chlorophenoxy-1-trans-butenyl)-3,5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ] and cyclopentane methylheptenoate-5-cis-2(3 $\alpha$ -hydroxy-4-m-chlorophenoxy-1-trans-butenyl)-3, 5 dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ] and the 9-and/or 11-and/or 15-esters of this compound. (The numbered designations in brackets refer to the positions on the cyclopentane ring.)

15

The following novel compounds may be used in the pharmaceutical compositions and the methods of treatment of the present invention.

20

- (1) cyclopentane heptenol-5-cis-2-(3 $\alpha$ -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ]
- 25 (2) cyclopentane heptenamide-5-cis-2-(3 $\alpha$ -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ]
- (3) cyclopentane N,N-dimethylheptenamide-5-cis-2-(3 $\alpha$ -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ]
- 30 (4) cyclopentane heptenyl methoxide-5-cis-2-(3 $\alpha$ -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ]

- (5) cyclopentane heptenyl ethoxide-5-cis-2-(3 $\alpha$ -hydroxy-4-meta-chlorophenoxy-1-trans-pentenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ]
- 5 (6) cyclopentane heptenylamide-5-cis-2-(3 $\alpha$ -hydroxy-4-metachlorophenoxy-1-trans-pentenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ]
- 10 (7) cyclopentane heptenylamide-5-cis-2-(3 $\alpha$ -hydroxy-4-trifluoromethylphenoxy-1-trans-pentenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ]
- 15 (8) cyclopentane N-isopropyl heptenamide-5-cis-2-(3 $\alpha$ -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ]
- (9) cyclopentane N-ethyl heptenamide-5-cis-2-(3 $\alpha$ -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5 dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ]
- 20 (10) cyclopentane N-methyl heptenamide-5-cis-2-(3 $\alpha$ -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ]
- 25 (11) cyclopentane heptenol-5-cis-2-(3 $\alpha$ -hydroxy-4-metachlorophenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ]
- 30 (12) cyclopentane heptenamide-5-cis-2-(3 $\alpha$ -hydroxy-4-metachlorophenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ]
- (13) cyclopentane heptenol-5-cis-2-(3 $\alpha$ -hydroxy-5-phenyl-1-trans-pentenyl)3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ]

5           A pharmaceutically acceptable salt is any salt which retains the activity of the parent compound and does not impart any deleterious or undesirable effect on the subject to whom it is administered and in the context in which it is administered. Such salts are those formed with pharmaceutically acceptable cations, e.g., alkali metals, alkali earth metals, etc.

10          Pharmaceutical compositions may be prepared by combining a therapeutically effective amount of at least one compound according to the present invention, or a pharmaceutically acceptable salt thereof, as an active ingredient, with conventional ophthalmically acceptable pharmaceutical excipients, and by preparation of unit dosage forms suitable for topical ocular use. The therapeutically efficient amount typically is between about 0.0001 and about 5% (w/v), preferably about 0.001 to about 1.0% (w/v) in liquid formulations.

15          For ophthalmic application, preferably solutions are prepared using a physiological saline solution as a major vehicle. The pH of such ophthalmic solutions should preferably be maintained between 4.5 and 8.0 with an appropriate buffer system, a neutral pH being preferred but not essential. The formulations may also contain conventional, pharmaceutically acceptable preservatives, stabilizers and surfactants.

20          Preferred preservatives that may be used in the pharmaceutical compositions of the present invention include, but are not limited to, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate and phenylmercuric nitrate. A preferred surfactant is, for example, Tween 80. Likewise, various preferred vehicles may be used in the ophthalmic preparations of the present invention. These vehicles include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose cyclodextrin and purified water.

25          Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium chloride, potassium chloride, mannitol and glycerin, or any other suitable ophthalmically acceptable tonicity adjustor.

30          Various buffers and means for adjusting pH may be used so long as the resulting preparation is ophthalmically acceptable.

Accordingly, buffers include acetate buffers, citrate buffers, phosphate buffers and borate buffers. Acids or bases may be used to adjust the pH of these formulations as needed.

5

In a similar vein, an ophthalmically acceptable antioxidant for use in the present invention includes, but is not limited to, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole and butylated hydroxytoluene.

10

Other excipient components which may be included in the ophthalmic preparations are chelating agents. The preferred chelating agent is edentate disodium, although other chelating agents may also be used in place of or in conjunction with it.

The ingredients are usually used in the following amounts:

<u>Ingredient</u>	<u>Amount (% w/v)</u>
active ingredient	about 0.001-5
preservative	0-0.10
vehicle	0-40
tonicity adjustor	0-10
buffer	0.01-10
pH adjustor	q.s. pH 4.5-7.5
antioxidant	as needed
surfactant	as needed
purified water	as needed to make 100%

15

The actual dose of the active compounds of the present invention depends on the specific compound, and on the condition to be treated; the selection of the appropriate dose is well within the knowledge of the skilled artisan.

20

The ophthalmic formulations of the present invention are conveniently packaged in forms suitable for metered application, such as in containers equipped with a dropper, to facilitate application to the eye. Containers suitable for dropwise application are usually made of suitable inert, non-toxic plastic material, and generally contain

between about 0.5 and about 15 ml solution. One package may contain one or more unit doses.

Especially preservative-free solutions are often formulated in non-resealable containers containing up to about ten, preferably up to about five units doses, where a typical unit dose is from one to about 8 drops, preferably one to about 3 drops. The volume of one drop usually is about 20-35 ml.

The invention is further illustrated by the following non-limiting Examples.

10

### Example 1

**Cyclopentane heptenoic acid, 5-cis-2-(3 $\alpha$ -hydroxy-4-m-chlorophenoxy-1-trans-buteneyl)-3,5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ]**

15

This compound may be purchased from Cayman Chemical Company of Ann Arbor, Michigan or synthesized by methods known in the art.

20

### **Example 2**

Cyclopentane methylheptenoate-5-cis-2  
(3 $\alpha$ -hydroxy-4-m-chlorophenoxy-1-trans-butenyl)  
-3, 5-dihydroxy, [1 $\alpha$ ,2 $\beta$ ,3 $\alpha$ ,5 $\alpha$ ]

25

To a stirred solution of cyclopentane heptenoic acid, 5-cis-2-(3 $\alpha$ -hydroxy-4-m-chlorophenoxy-1-trans-butenyl)-3,5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ](24 mg. 0.0565 mmol) in acetone (0.6 ml) at room temperature was added 1, 8-diazabicyclo [5.4.0.] undec-7-ene (DBU) (40, ul, 0.27 mmol) and methyl iodide (20 ul, 0.32 mmol). The reaction turned yellow with the DBU addition. The reaction was maintained at room temperature for 6.5 hours, then was diluted with ethyl acetate (30 ml) and filtered through a plug of celite with the aid of ethyl acetate. After concentration *in vacuo*, the residue was flushed with ethylacetate (EtOAc) through a 20 mm x 160 mm column of silica to give the desired methyl ester.

Example 3

5

Cyclopentane heptenamide-5-cis-2-  
(3 $\alpha$ -hydroxy-4-m-chlorophenoxy-1-trans-butenyl)  
-3, 5-dihydroxy, [1 $\alpha$ .2 $\beta$ .3 $\alpha$ .5 $\alpha$ ]

10

A mixture of the methyl ester of the compound of Example 1 (9.2 mg, 0.0222 mmol) and NH<sub>4</sub>Cl (10 mg, 0.187 mmol) in NH<sub>3</sub> was heated at 80°C for 12 hours. After cooling to room temperature, the solvents were evaporated and the residue was subjected to column chromatography to provide the named amide as 7.2 mg of a clear, colorless liquid.

15

Example 4

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Cyclopentane heptenoic acid-5-cis2-(3 $\alpha$ -hydroxyl-4-m-trifluoromethylphenoxy-1-trans-butenyl)-3,5-dihydroxy [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ]

This compound may be purchased from Cayman Chemical Company of Ann Arbor, Michigan or synthesized by methods known in the art.

Example 5

25

Cyclopentane heptenamide-5-cis2-(3 $\alpha$ -hydroxyl-4-m-trifluoromethylphenoxy-1-trans-butenyl)-3,5-dihydroxy [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ]

30

A mixture of the methyl ester of the compound of Example 4 (fluprostenol) and NH<sub>4</sub>Cl in NH<sub>3</sub> is heated at 80°C for 12 hours. After cooling to room temperature the solvents are evaporated and the residue is subjected to column chromatography to provide the named amide.

35

Example 6

Measurement of intraocular pressure studies in dogs involved pneumatonometry performed in conscious, Beagle dogs of both sexes (10-15 kg). The animals remained conscious throughout the study and were gently restrained by hand. Drugs were administered topically to one eye as a 25 µL volume drop, the other eye received 25 µL vehicle (0.1% polysorbate 80:10 mM TRIS) as a control. 0.1% proparacaine was used for corneal anesthesia during tonometry. Intraocular pressure was determined just before drug administration and at 2, 4 and 6 hour thereafter on each day of the 5 day study. Drug was administered twice a day, with a 6 hour interval between doses that spanned the intraocular pressure measurement time frame. The result reported in Table 1, below.

15

**Table 1.** Comparison of effects of certain compounds of the invention on dog intraocular pressure. Values indicate mean changes from baseline introcular pressure ( $\pm$  SEM) at predetermined times post-dosing. n=8, \*p<0.05, \*\*p<0.01.

20

**INTRAOCULAR PRESSURE (mmHg) CHANGE AT  
PREDETERMINED TIMES (HR)**

	<u>COMPOUND</u>	<u>DOSE%</u>	2	4	6	24
25	Example 1	0.01	-0.1 $\pm$ 0.8	-5.2 $\pm$ 1.4**	-4.3 $\pm$ 0.8	-4.4 $\pm$ 0.8
	Example 1	0.1	-3.1 $\pm$ 0.8**	-3.2 $\pm$ 0.7	-2.7 $\pm$ 0.8	-
30	Example 3	0.01	-2.2 $\pm$ 1.0*	5.5 $\pm$ 1.1**	-4.0 $\pm$ 1.4*	2.7 $\pm$ 1.1*
	Example 3	0.1	-1.3 $\pm$ 0.4*	2.3 $\pm$ 0.7**	-2.6 $\pm$ 0.6**	-
35	Example 5	0.1	-2.7 $\pm$ 0.8*	-3.4 $\pm$ 0.9*	-2.8 $\pm$ 0.4**	-2.1 $\pm$ 1.6*

Example 4	0.01	-0.9±0.7	-2.5±0.7*	-3.2±0.7**	-1.3±0.7
Fluprostenol	0.1	-1.3±0.1	-2.1±1.1	-2.7±1.3	-3.1±0.9*

Example 7

5

Measurement of ocular surface hyperemia was visually assessed and scored according to the following schematic:

	<u>Hyperemia Score</u>	<u>Assigned Value</u>
	<1	1
	1 slight	2
	>1<2	3
10	2 moderate	4
15	>2>3	5
	3 severe	6
	(baseline scores for dogs are typically < 1)	
20	The hyperemia value for each dog at a single time point (x) is obtained as follows: (treated eye value at hr x - baseline value)-(control eye value at hr x-baseline value). A composite value is then obtained by dividing the sum of the post-treatment measurement at each time point by the number of animals in the group: i.e. $m$ where $m = \frac{\sum x}{n}$	
25	measurements of ocular surface hyperemia. Ocular surface hyperemia is evaluated at the same time points as intraocular pressure measurement. It should be noted that untreated dog eyes frequently have a pink/red tone. Thus, values of <1 and 1 are essentially within the normal range. The results are reported in Table 2, below.	
30		

**Table 2.** Comparison of effects of certain compounds of the invention on dog ocular surface hyperemia. Values are composite scores as indicated in the methods.

	<u>COMPOUND</u>	<u>DOSE%</u>	<u>OCULAR SURFACE HYPEREMIA: COMPOSITE SCORE</u>
10	Example 1	0.01	-
10	Example 1	0.1	0.33
15	Example 3	0.01	-
15	Example 3	0.1	0.81
20	Example 5	0.1	0.81
20	Example 4	0.01	1.08
	Fluprostenol	0.1	1.50

It is clear that the compounds of Examples 1, 3 and 5, unexpectedly, show better efficacy at lowering IOP than Example 4 while showing less hyperemia.

The compounds of the invention may also be useful in the treatment of various pathophysiological diseases including acute myocardial infarction, vascular thrombosis, hypertension, pulmonary hypertension, ischemic heart disease, congestive heart failure, and angina pectoris, in which case the compounds may be administered by any means that effect vasodilation and thereby relieve the symptoms of the disease. For example, administration may be by oral, transdermal, parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, or buccal routes.

The compounds of the invention may be used alone, or in combination with other of the known vasodilator drugs.

The compounds of the invention may be formulated into an ointment containing about 0.10 to 10% of the active ingredient in a suitable base of, for example, white petrolatum, mineral oil and

petroatum and lanolin alcohol. Other suitable bases will be readily apparent to those skilled in the art.

The pharmaceutical preparations of the present invention are manufactured in a manner which is itself known, for example, by means of conventional dissolving or suspending the compounds, which are all either water soluble or suspendable. For administration in the treatment of the other mentioned pathophysiological disorders. The pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer such as glycerol or sorbitol. The push-fit capsules can contain the active compounds in liquid form that may be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids, such as in buffered salt solution. In addition, stabilizers may be added.

In addition to being provided in a liquid form, for example in gelatin capsule or other suitable vehicle, the pharmaceutical preparations may contain suitable excipients to facilitate the processing of the active compounds into preparations that can be used pharmaceutically. Thus, pharmaceutical preparations for oral use can be obtained by adhering the solution of the active compounds to a solid support, optionally grinding the resulting mixture and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.

Suitable excipients are, in particular, fillers such as sugars, for example lactose or sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, as well as binders such as starch, paste using for example, maize starch, wheat starch, rich starchy, potato starch, gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, disintegrating agents may be added such as the above-mentioned starches and also carboxymethyl-starch, crosslinked polyvinyl pyrrolidone, agar, or

algenic acid or a salt thereof, such as sodium alginate. Auxiliaries are, above all, flow-regulating agents and lubricants, for example, silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores are  
5 provided with suitable coatings which if desired, are resistant to gastric juices. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order  
10 to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations such as acetylcellulose phthalate or hydroxypropylmethyl-cellulose phthalate, are used. Dye stuffs or pigments may be added to the tables or dragee coatings, for example, for identification or in order to characterize combinations of active  
15 compound doses.

Suitable formulations for intravenous or parenteral administration include aqueous solutions of the active compounds. In addition, suspensions of the active compounds as oily injection suspensions may be administered. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension include, for example, sodium carboxymethyl cellulose, sorbitol, and/or dextran. Optionally, the suspension may also contain  
20 stabilizers.

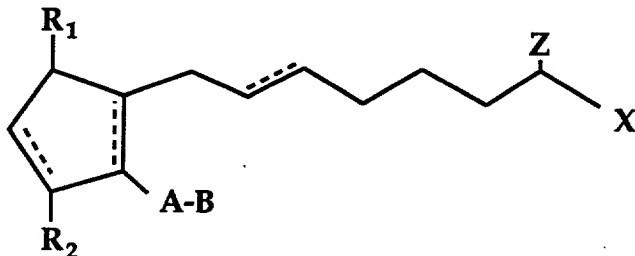
The foregoing description details specific methods and compositions that can be employed to practice the present invention, and represents the best mode contemplated. However, it is apparent for one of ordinary skill in the art that further compounds with the desired pharmacological properties can be prepared in an analogous manner, and that the disclosed compounds can also be obtained from different starting compounds via different chemical reactions. For  
25 example, the present invention contemplates certain prodrugs of the

above disclosed compounds, wherein R<sup>4</sup> is R<sup>5</sup>-C- or R<sup>5</sup>-O-C-. These compounds may be made by acylation or esterification of the corresponding hydroxy or amino derivative. Similarly, different pharmaceutical compositions may be prepared and used with  
30  
35

substantially the same result. Thus, however detailed the foregoing may appear in text, it should not be construed as limiting the overall scope hereof; rather, the ambit of the present invention is to be governed only by the lawful construction of the appended claims.

CLAIMS

1. A method of treating ocular hypertension which comprises applying to the eye an amount sufficient to treat ocular hypertension of a compound of formula I

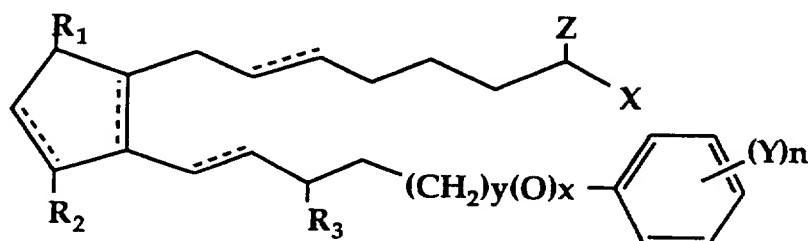


wherein the dashed bonds represent a single or double bond which can be in the cis or trans configuration, A is an alkylene or alkenylene radical having from two to six carbon atoms, which radical may be interrupted by one or more oxide radicals and substituted with one or more hydroxy, oxo, alkyloxy or alkylcarboxy groups wherein said alkyl radical comprises from one to six carbon atoms; B is a cycloalkyl radical having from three to seven carbon atoms, or an aryl radical, selected from the group consisting of hydrocarbyl aryl and heteroaryl radicals having from four to ten carbon atoms wherein the heteroatom is selected from the group consisting of nitrogen, oxygen and sulfur atoms; X is a radical selected from the group consisting of -OR<sup>4</sup> and -N(R<sup>4</sup>)<sub>2</sub> wherein R<sup>4</sup> is selected from the group consisting of hydrogen, a lower alkyl radical having from one to six

carbon atoms, R<sup>5</sup>-C=O or R<sup>5</sup>-O-C=O wherein R<sup>5</sup> is a lower alkyl radical having from one to six carbon atoms; Z is =O or represents 2 hydrogen radicals; one of R<sub>1</sub> and R<sub>2</sub> is =O, -OH or a -O(CO)R<sub>6</sub> group, and the other one is -OH or -O(CO)R<sub>6</sub>, or R<sub>1</sub> is =O and R<sub>2</sub> is H, wherein R<sub>6</sub> is a saturated or unsaturated acyclic hydrocarbon group having from 1 to about 20 carbon atoms, or -(CH<sub>2</sub>)<sub>m</sub>R<sub>7</sub> wherein m is 0-10, and R<sub>7</sub> is cycloalkyl radical, having from three to seven carbon atoms, or a hydrocarbyl aryl or heteroaryl radical, as defined above, or a pharmaceutically-acceptable salt thereof, provided however that

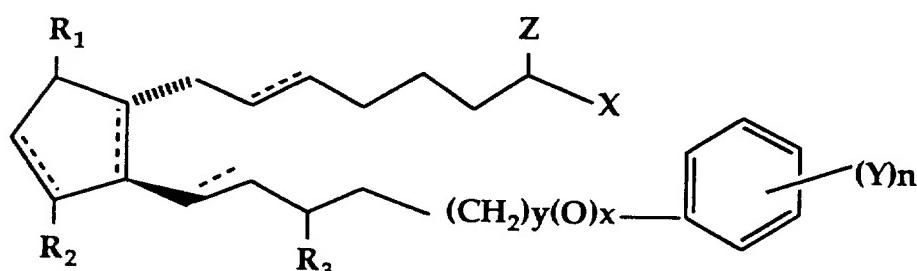
when B is not substituted with a pendant heteroatom-containing radical and Z is =O, then X is not -OR<sup>4</sup>.

- 5 2. The method of Claim 1 wherein said compound is a represented by the formula (II)



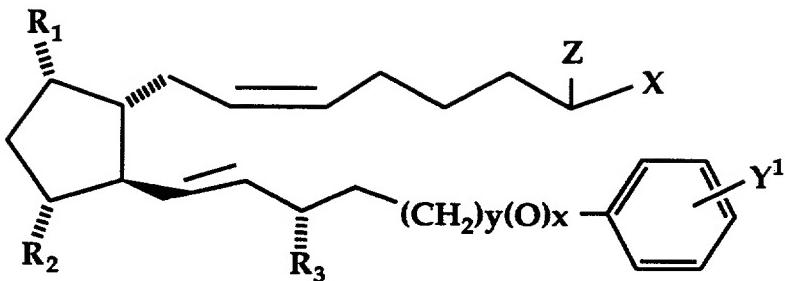
10 wherein y is 0 or 1, x is 0 or 1 and x+ y are not both 1, Y is a radical selected from the group consisting of alkyl, halo, nitro, amino, thiol, hydroxy, alkyloxy, alkylcarboxy and halosubstituted alkyl, wherein said alkyl radical comprises from one to six carbon atoms, n is 0 or an integer of from 1 to 3 and R<sub>3</sub> is =O, -OH or -O(CO)R<sub>6</sub>.

- 15 3. The method of claim 2 wherein said compound is represented by formula III.



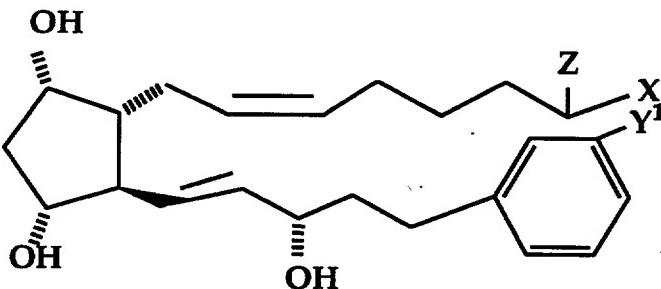
wherein hatched lines indicate the  $\alpha$  configuration and solid triangles indicate the  $\beta$  configuration.

- 20 4. The method of claim 3 wherein said compound is represented by the formula IV.



wherein Y<sup>1</sup> is Cl or trifluoromethyl.

5. The method of claim 4 wherein said compound is a  
represented by the formula V



and the 9- and/or 11- and/or 15 esters, thereof.

- 10 6. The method of claim 5 wherein Z is =O and X is selected from the group consisting of NH<sub>2</sub> or OCH<sub>3</sub>.
7. The method of claim 5 wherein Y is O, Z is =O and X is selected from the group consisting of alkoxy and amido radicals.
- 15 8. The method of claim 1 wherein said compound is selected from the group consisting of:

20 cyclopentane heptenol-5-cis-2-(3 $\alpha$ -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ];

cyclopentane heptenamide-5-cis-2-(3 $\alpha$ -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ];

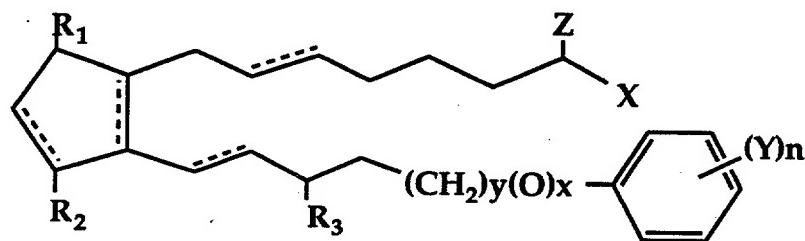
- cyclopentane N,N-dimethylheptenamide-5-cis-2-(3 $\alpha$ -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ];
- 5 cyclopentane heptenyl methoxide-5-cis-2-(3 $\alpha$ -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ];
- cyclopentane heptenyl ethoxide-5-cis-2-(3 $\alpha$ -hydroxy-4-meta-chlorophenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ];
- 10 cyclopentane heptenylamide-5-cis-2-(3 $\alpha$ -hydroxy-4-meta-chlorophenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ];
- 15 cyclopentane heptenylamide-5-cis-2-(3 $\alpha$ -hydroxy-4-meta-trifluoromethyl-phenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ];
- cyclopentane N-isopropyl heptenamide-5-cis-2-(3 $\alpha$ -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ];
- 20 cyclopentane N-ethyl heptenamide-5-cis-2-(3 $\alpha$ -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ];
- 25 cyclopentane N-methyl heptenamide-5-cis-2-(3 $\alpha$ -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ];
- cyclopentane heptenol-5-cis-2-(3 $\alpha$ -hydroxy-4-m-chlorophenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ];
- 30 cyclopentane heptenamide-5-cis-2-(3 $\alpha$ -hydroxy-4-m-chlorophenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ] and  
cyclopentane heptenol-5-cis-2-(3 $\alpha$ -hydroxy-5-phenylpentyl)3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ]

9. The method of claim 7 wherein X is selected from the group consisting of NH<sub>2</sub> and OCH<sub>3</sub>.
10. The method of claim 1 wherein said compound is selected from the group consisting of:
- cyclopentane heptenoic acid-5-cis-2-(3 $\alpha$ -hydroxy-4-meta-chlorophenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ];
- cyclopentane heptenylamide-5-cis-2-(3 $\alpha$ -hydroxy-4-meta-chlorophenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ];
- cyclopentane heptenylamide-5-cis-2-(3 $\alpha$ -hydroxy-4-meta-trifluoromethylphenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ]; and
- cyclopentane heptenonic acid-5-cis-2-(3 $\alpha$ -hydroxy-4-meta-trifluoromethyl-phenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ].
11. A method of treating cardiovascular pulmonary-respiratory, gastrointestinal, reproductive and allergic diseases and shock in a human which comprises administering to said human an effective amount of a compound of formula I
- 
- wherein the dashed bonds represent a single or double bond which can be in the cis or trans configuration, A is an alkylene or alkenylene radical having from two to six carbon atoms, which radical may be interrupted by one or more oxide radicals and substituted with one or more hydroxy, oxo, alkyloxy or alkylcarboxy groups wherein said alkyl radical comprises from one to six carbon

atoms, or an aryl radical, selected from the group consisting of hydrocarbyl aryl and heteroaryl radicals having from four to ten carbon atoms wherein the heteroatom is selected from the group consisting of nitrogen, oxygen and sulfur atoms; X is a radical selected from the group consisting of -OR<sup>4</sup> and -N(R<sup>4</sup>)<sub>2</sub> wherein R<sup>4</sup> is selected from the group consisting of hydrogen, a lower alkyl radical having from one to six

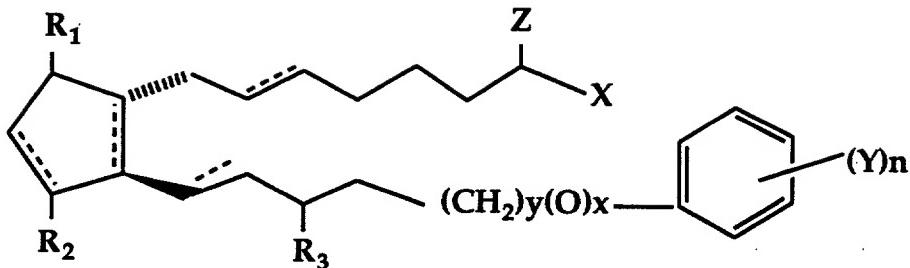
10 carbon atoms,  $R^5-C-$  or  $R^5-O-C-$  wherein  $R^5$  is a lower alkyl radical having from one to six carbon atoms; Z is =O or represents 2 hydrogen radicals; one of  $R_1$  and  $R_2$  is =O, -OH or a -O(CO) $R_6$  group, and the other one is -OH or -O(CO) $R_6$ , or  $R_1$  is =O and  $R_2$  is H, wherein  $R_6$  is a saturated or unsaturated acyclic hydrocarbon group having from 1 to about 20 carbon atoms, or -(CH<sub>2</sub>)<sub>m</sub> $R_7$  wherein m is 0-10, and  $R_7$  is cycloalkyl radical, having from three to seven carbon atoms, or a hydrocarbyl aryl or heteroaryl radical, as defined above, or a pharmaceutically-acceptable salt thereof, provided however that when B is not substituted with a pendant heteroatom-containing radical and Z is =O, then X is not -OR<sup>4</sup>

20        12. The method of Claim 1 wherein said compound is a represented by the formula (II)



25 wherein y is 0 or 1, x is 0 or 1 and x+y are not both 1, Y is a radical selected from the group consisting of alkyl, halo, nitro, amino, thiol, hydroxy, alkyloxy, alkylcarboxy and halosubstituted alkyl, wherein said alkyl radical comprises from one to six carbon atoms, n is 0 or an integer of from 1 to 3 and R<sub>3</sub> is =O, -OH or -O(CO)R<sub>6</sub>.

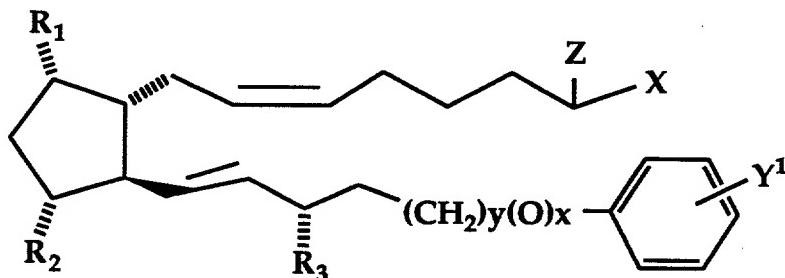
30 13. The method of claim 2 wherein said compound is represented by formula III.



wherein hatched lines indicate the  $\alpha$  configuration and solid triangles indicate the  $\beta$  configuration.

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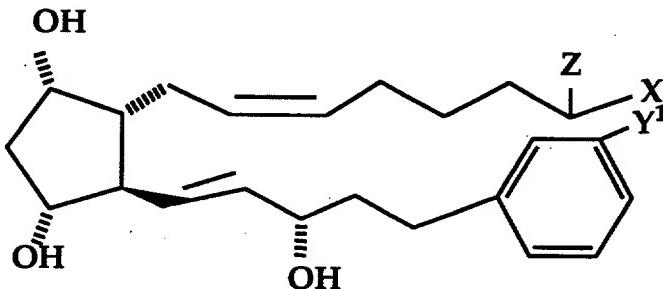
14. The method of claim 3 wherein said compound is represented by the formula IV.



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wherein  $\text{Y}^1$  is Cl or trifluoromethyl.

15. The method of claim 4 wherein said compound is a represented by the formula V



15

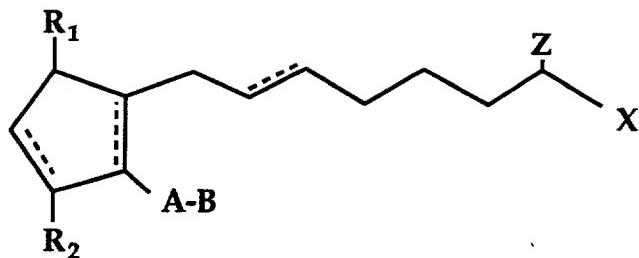
and the 9- and/or 11- and/or 15 esters, thereof.

16. The method of claim 5 wherein Z is =O and X is selected from the group consisting of  $\text{NH}_2$  or  $\text{OCH}_3$ .

20

17. The method of claim 5 wherein Y is O, Z is =O and X is selected from the group consisting of alkoxy and amido radicals.
18. The method of claim 1 wherein said compound is selected from the group consisting of:
- 5 cyclopentane heptenol-5-cis-2-(3 $\alpha$ -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ];
- 10 cyclopentane heptenamide-5-cis-2-(3 $\alpha$ -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ];
- cyclopentane N,N-dimethylheptenamide-5-cis-2-(3 $\alpha$ -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ];
- 15 cyclopentane heptenyl methoxide-5-cis-2-(3 $\alpha$ -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ];
- cyclopentane heptenyl ethoxide-5-cis-2-(3 $\alpha$ -hydroxy-4-meta-chlorophenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ];
- 20 cyclopentane heptenylamide-5-cis-2-(3 $\alpha$ -hydroxy-4-meta-chlorophenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ];
- cyclopentane heptenylamide-5-cis-2-(3 $\alpha$ -hydroxy-4-meta-trifluoromethyl-phenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ];
- 25 cyclopentane N-isopropyl heptenamide-5-cis-2-(3 $\alpha$ -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ];
- cyclopentane N-ethyl heptenamide-5-cis-2-(3 $\alpha$ -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ];
- 30 cyclopentane N-methyl heptenamide-5-cis-2-(3 $\alpha$ -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ];

- cyclopentane N-methyl heptenamide-5-cis-2-(3 $\alpha$ -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ];
- 5      cyclopentane heptenol-5-cis-2-(3 $\alpha$ -hydroxy-4-m-chlorophenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ];
- 10     cyclopentane heptenamide-5-cis-2-(3 $\alpha$ -hydroxy-4-m-chlorophenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ] and
- 10     cyclopentane heptenol-5-cis-2-(3 $\alpha$ -hydroxy-5-phenylpentyl)3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ]
- 15    19. The method of claim 7 wherein X is selected from the group consisting of NH<sub>2</sub> and OCH<sub>3</sub>.
- 15    20. The method of claim 1 wherein said compound is selected from the group consisting of:
- 20     cyclopentane heptenoic acid-5-cis-2-(3 $\alpha$ -hydroxy-4-meta-chlorophenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ];
- 20     cyclopentane heptenylamide-5-cis-2-(3 $\alpha$ -hydroxy-4-meta-chlorophenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ];
- 25     cyclopentane heptenylamide-5-cis-2-(3 $\alpha$ -hydroxy-4-meta-trifluoromethylphenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ]; and
- 30     cyclopentane heptenonic acid-5-cis-2-(3 $\alpha$ -hydroxy-4-meta-trifluoromethylphenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ].
- 35    21. A compound useful for treating cardiovascular pulmonary-respiratory, gastrointestinal, reproductive and allergic diseases and



wherein the dashed bonds represent a single or double bond which can be in the cis or trans configuration, A is an alkylene or alkenylene radical having from two to six carbon atoms, which radical may be interrupted by one or more oxide radicals and substituted with one or more hydroxy, oxo, alkyloxy or alkylcarboxy groups wherein said alkyl radical comprises from one to six carbon atoms; B is a cycloalkyl radical having from three to seven carbon atoms, or an aryl radical, selected from the group consisting of hydrocarbyl aryl and heteroaryl radicals having from four to ten carbon atoms wherein the heteroatom is selected from the group consisting of nitrogen, oxygen and sulfur atoms; X is a radical selected from the group consisting of -OR<sup>4</sup> and -N(R<sup>4</sup>)<sub>2</sub> wherein R<sup>4</sup> is selected from the group consisting of hydrogen, a lower alkyl radical having from one to six

carbon atoms, R<sup>5</sup>-C- or R<sup>5</sup>-O-C- wherein R<sup>5</sup> is a lower alkyl radical having from one to six carbon atoms; Z is =O or represents 2 hydrogen radicals; one of R<sub>1</sub> and R<sub>2</sub> is =O, -OH or a -O(CO)R<sub>6</sub> group, and the other one is -OH or -O(CO)R<sub>6</sub>, or R<sub>1</sub> is =O and R<sub>2</sub> is H, wherein R<sub>6</sub> is a saturated or unsaturated acyclic hydrocarbon group having from 1 to about 20 carbon atoms, or -(CH<sub>2</sub>)<sub>m</sub>R<sub>7</sub> wherein m is 0-10, and R<sub>7</sub> is cycloalkyl radical, having from three to seven carbon atoms, or a hydrocarbyl aryl or heteroaryl radical, as defined above, or a pharmaceutically-acceptable salt thereof, provided however that when B is not substituted with a pendant heteroatom-containing radical and Z is =O, then x is not -OR<sup>4</sup>.

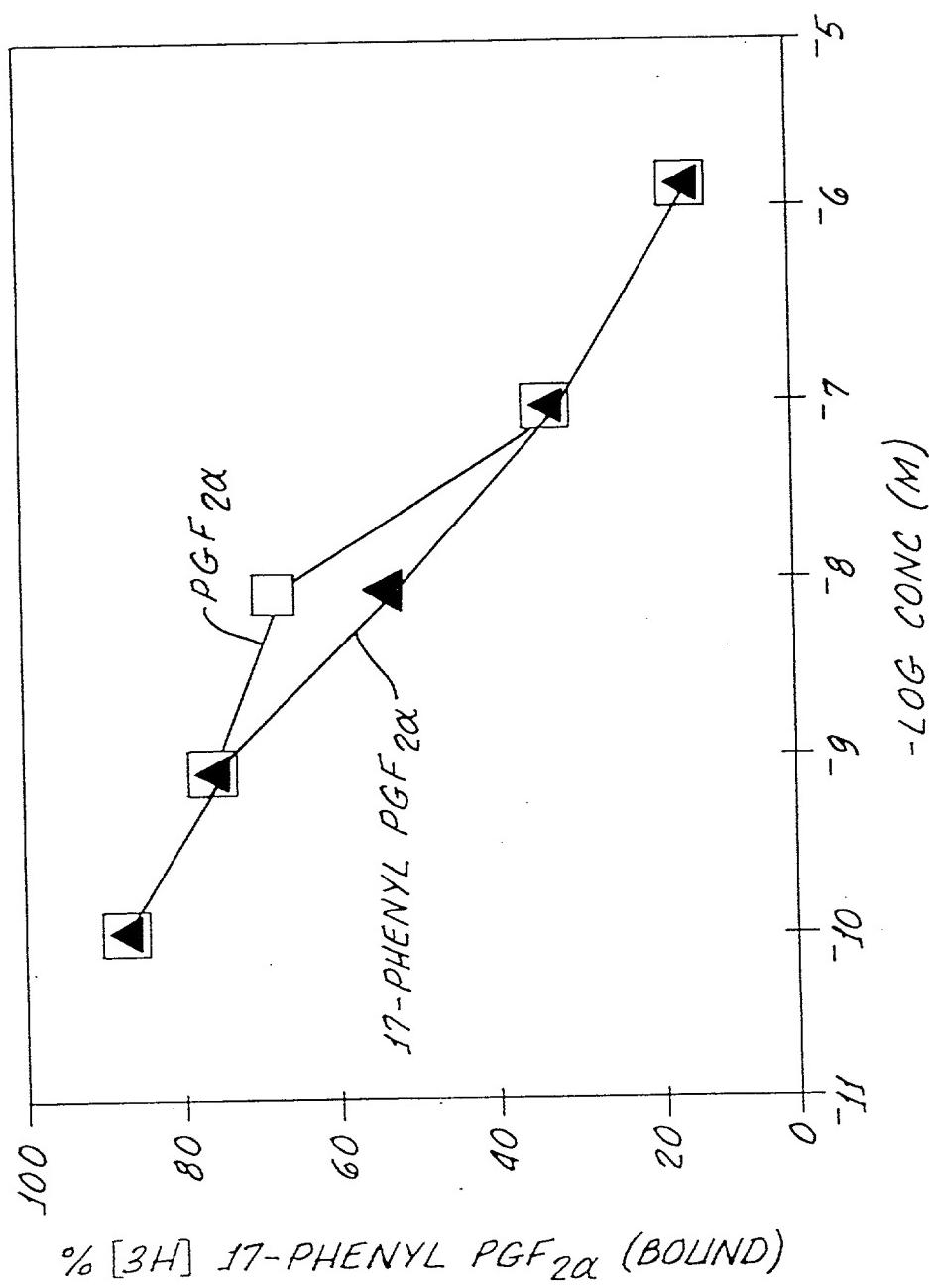
22. The compound of claim 21 wherein said compound is selected from the group consisting of
- 5      cyclopentane heptenoic acid-5-cis-2-(3 $\alpha$ -hydroxy-4-meta-chloro-phenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ];
- cyclopentane heptenylamide-5-cis-2-(3 $\alpha$ -hydroxy-4-meta-chloro-phenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ]; and
- 10     cyclopentane heptenylamide-5-cis-2-(3 $\alpha$ -hydroxy-4-metatrifluoromethylphenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 $\alpha$ , 2 $\beta$ , 3 $\alpha$ , 5 $\alpha$ ].
- 15     23. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 21 in admixture with a non-toxic, pharmaceutically acceptable liquid vehicle.
- 20     24. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 22 in admixture with a non-toxic, pharmaceutically acceptable liquid vehicle.
- 25     25. A method of treating ocular hypertension which comprises applying to the eye an amount sufficient to treat ocular hypertension of a compound selected from the group consisting of cloprostenol, fluprostenol and their pharmaceutically acceptable esters and salts.

## **ABSTRACT**

The present invention provides cyclopentane heptanoic acid, 2-cycloalkyl or arylalkyl compounds, which may be substituted in the 1-position with amino, amido, ether or ester groups, e.g., a 1-OH cyclopentane heptanoic acid, 2-(cycloalkyl or arylalkyl) compound. The cyclopentane heptanoic acid, 2-(cycloalkyl or arylalkyl) compounds of the present invention are potent ocular hypotensives, and are particularly suitable for the management of glaucoma.

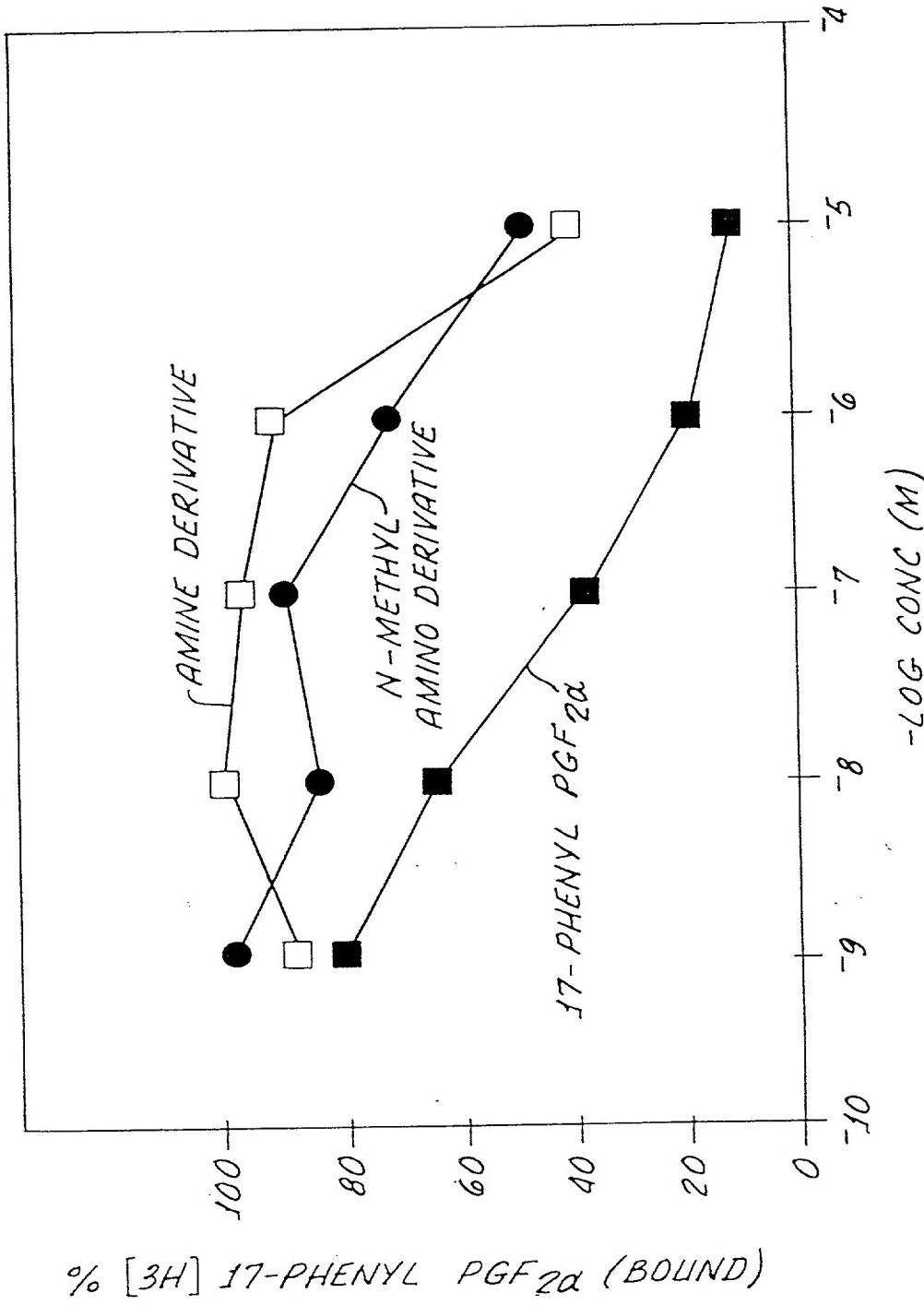
Moreover, the cyclopentane heptanoic, 2-(cycloalkyl or arylalkyl) compounds of this invention are smooth muscle relaxants with broad application in systemic hypertensive and pulmonary diseases; smooth muscle relaxants with application in gastrointestinal disease, reproduction, fertility, incontinence, shock, etc.

FIG. 1.



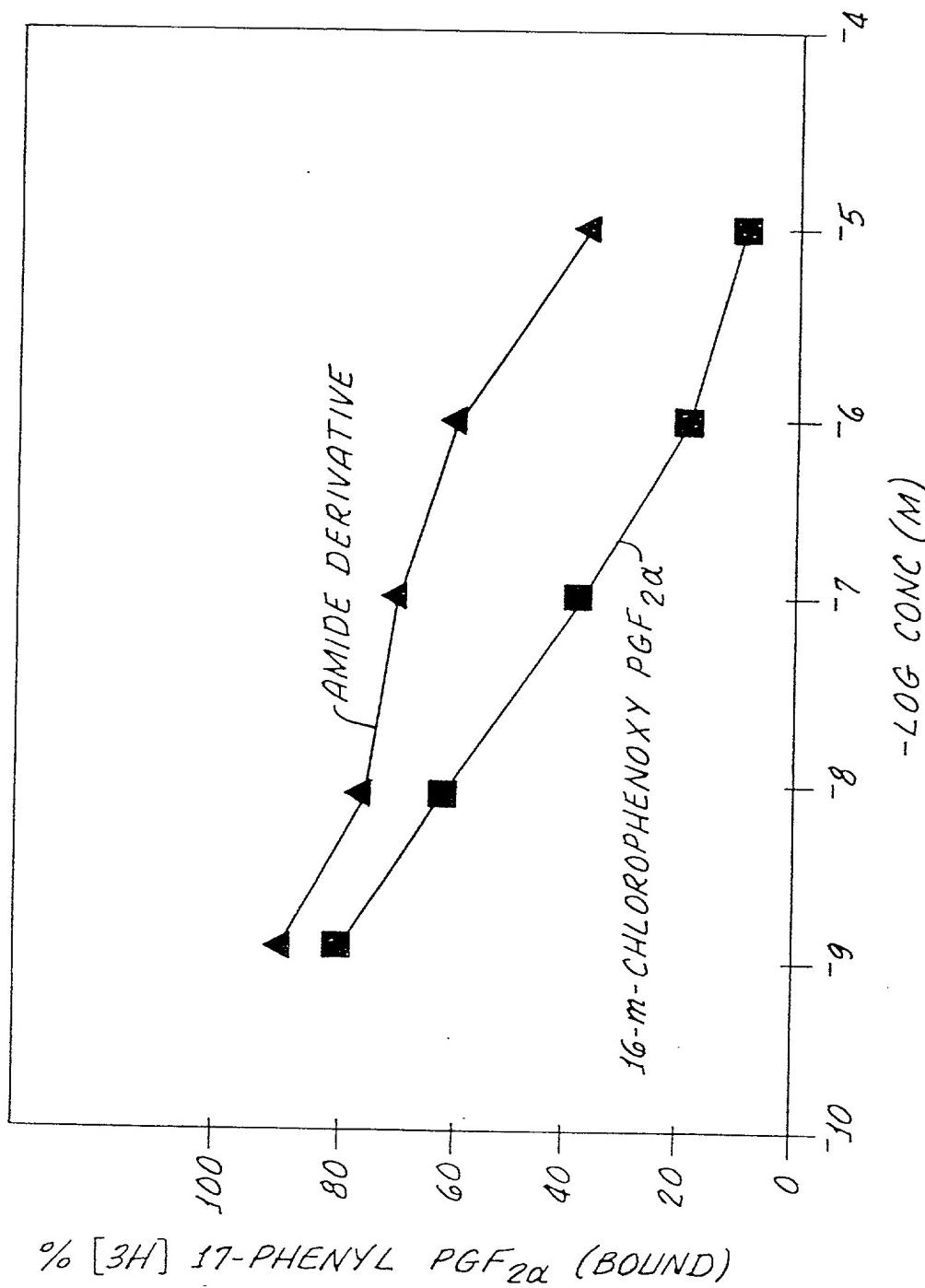
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FIG. 2.



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Fig. 3.



**DECLARATION - U.S.A Application**

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am an original, first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled NON-ACIDIC CYCLOPENTANE HEPTANOIC ACID, 2-CYCLOALKYL OR ARYLALKYL DERIVATIVES AS THERAPEUTIC AGENTS.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, Section 1.56(a).

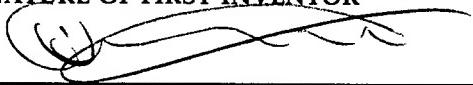
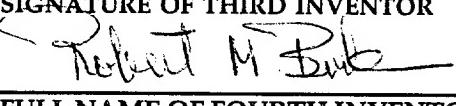
I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application (s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

I hereby appoint Robert Baran, Registration No. 25,806, Martin A. Voet; Registration No. 25,208; and Howard R. Lambert, Registration No. 27,206, as attorneys to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

SEND CORRESPONDENCE TO AND DIRECT TELEPHONE CALLS TO:

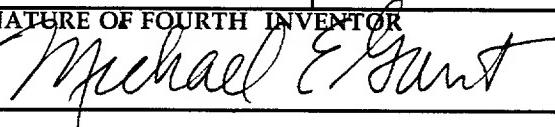
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I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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<b>FULL NAME OF FOURTH INVENTOR:</b>		

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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